Hormesis as a Biological Hypothesis

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A comprehensive effort was undertaken to identify articles demonstrating chemical hormesis. Nearly 4000 potentially relevant articles were retrieved from preliminary computer database searches by using various key word descriptors and extensive cross-referencing. A priori evaluation criteria were established including study design features (e.g., number of doses, dose range), statistical analysis, and reproducibility of results. Evidence of chemical hormesis was judged to have occurred in approximately 350 of the 4000 studies evaluated. Chemical hormesis was observed in a wide range of taxonomic groups and involved agents representing highly diverse chemical classes, many of potential environmental relevance. Numerous biological end points were assessed; growth responses were the most prevalent, followed by metabolic effects, longevity, reproductive responses, and survival. Hormetic responses were generally observed to be of limited magnitude. The average low-dose maximum stimulation was approximately 50% greater than controls. The hormetic dose–response range was generally limited to about one order of magnitude, with the upper end of the hormetic curve approaching the estimated no observable effect level for the particular end point. Based on the evaluation criteria, high to moderate evidence of hormesis was observed in studies comprised of > 6 doses; with > 3 doses in the hormetic zone. The present analysis suggests that chemical hormesis is a reproducible and relatively common biological phenomenon. A quantitative scheme is presented for future application to the database. — *Environ Health Perspect* 106(Suppl 1):357–362 (1998). http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-1/357-362calabrese/abstract.html

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Introduction

The concept of chemical hormesis has a long history, originating over a century ago from the research of Schulz (*1*), who noted that many chemicals were able to stimulate growth and respiration of yeast at low doses but were inhibitory at higher levels. This concept of a generalized low-dose stimulation–high-dose inhibition was gradually supported by similar observations with other chemicals and eventually became known as the Arndt–Schulz law. Although Schulz (*1*) ushered in the so-called modern

concept of hormesis, Paracelsus (*2*), writing in the 16th century, likewise noted that various toxic substances may be beneficial in small quantities.

Despite the widespread recognition of apparent hormetic effects, which continued into the early decades of the 20th century, Stebbing (*2*) argues that the Arndt–Schulz law gradually fell into disuse because it did not provide an adequate explanatory (i.e., mechanism-based) capacity. Nonetheless, over the years a continuing stream of observations has been reported (*2*) in toxicological publications and the broader biological literature that document low-dose stimulations.
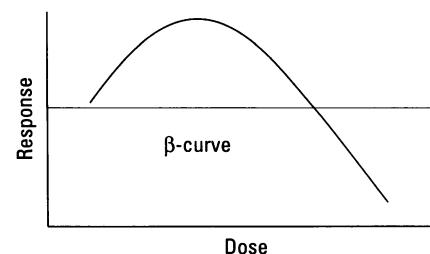
Although there has been long-standing interest in the concept of chemical hormesis few attempts have been made to summarize the extent of its occurrence in biological systems and its potential to generalize with respect to animal models, biological end points, or chemical class. Previous limited summaries have been reported (*2–6*). In addition, Davis and Svendsgaard (*7*) attempted to assess the statistical likelihood of low-dose stimulation among a random sample of experimental studies published in

prominent toxicological journals. The goal of this research was to extend the findings of these previous reports by attempting to evaluate in a comprehensive manner those studies that are believed or alleged to display evidence of chemical hormesis. These findings would then be employed to assess the scientific basis of the hypothesis that hormesis is induced by chemical agents and is a generalized biological phenomenon.

Criteria for Evaluating Hormesis

To conduct this investigation it was necessary to define chemical hormesis and develop a priori criteria to evaluate its possible occurrence in experimental or empirical investigations. The definition derived from Stebbing (*2*) is low-dose stimulation followed by higher-dose inhibition; the most common form of hormesis follows the widely recognized β-curve (Figure 1). The use of the β-curve follows principally from the widespread use of growth as a principal end point in hormesis research. However, the term U shaped, as emphasized by Davis and Svendsgaard (*8*), would most appropriately be applied when the end point relates to a traditional toxicologically based health end point such as cancer incidence. The criteria applied in the present methodology were the same for the β-curve and U-shaped relationships.

Because hormesis is a scientific hypothesis the question of whether it is beneficial is often contextual. To eliminate subjective decisions concerning beneficial versus harmful effects, the decision was made to evaluate model- and end point-specific responses with respect to stimulation and inhibition. For example, stimulation of detoxifying enzyme levels observed in the larval form of a species would be evaluated for its hormetic potential even though this increased metabolic activity, although beneficial in the short-term, may have a detrimental effect on

Figure 1. The most common dose–response curve showing hormesis—the β-curve.

other end points. Likewise the stimulation of microbial reproduction by antibiotics was evaluated for its hormetic potential even though these low dose effects are harmful to the host organism.

This assessment of chemical hormesis has been restricted to those dose–response relationships most conforming to the β-curve and would be affected by the magnitude of the low-dose stimulatory response, the number of doses establishing the reliability of the β-curve, the presence of statistical analysis, and the reproducibility of the findings. Within this category only the well-known types of dose–response relationships exhibiting β- or U-shaped curves (represented by nutritionally essential substances, with the exception of copper) were excluded, as this phenomenon is generally accepted.

The capacity to evaluate high conformity to the β-curve ideally requires the establishment of an end point-specific lowest observable effect level (LOEL) and no observable effect level (NOEL), with multiple doses within two orders of magnitude immediately below the NOEL. This suggests that to be a relevant study for the evaluation of chemical hormesis, an experiment would be expected to have four or more doses distributed in a highly specific manner relative to the NOEL. Therefore, highly restrictive study design requirements must be satisfied to adequately assess chemical hormesis. Most toxicological studies do not satisfy these design criteria and would be classified as nonrelevant, as they are unable to demonstrate no evidence or some evidence (i.e., equal to or greater than low evidence) of hormesis. Similarly, data from epidemiological studies, with the exception of reports on ethanol and cardiovascular disease, were difficult to conform to these criteria. Within this evaluative context judgment on the evidence supporting consistency of data from an individual experiment with the definition of chemical hormesis was made by a weight-of-evidence procedure. It should be noted that upward-curving β- or U-shaped dose–response curves (e.g., characteristic of certain studies where low doses reduce mortality) were included in the analysis. In addition many studies contain multiple dose–response relationships for the same or different end points. In these cases all end points within a study showing low-dose stimulation were evaluated.

To facilitate an appreciation of weight-of-evidence evaluation methodology, several graphic examples are presented

that illustrate how such judgments concerning chemical hormesis may be made (Figure 2A–E).

Figure 2A depicts a hypothetical study with a dose range of 10-fold that displays a modest statistically insignificant increase (i.e., stimulation) in response at the lowest dose followed by a more definitive decrease (i.e., inhibition). Using the criteria applied in the present methodology this study would be judged as a) displaying an extremely limited dosage range probably inadequate for assessment of the dynamics of the dose–response continuum, b) inadequately describing the dose–response relationship in the hypothetical hormetic zone, and c) having inadequate statistical power to conclude that the stimulatory effort was treatment related. An initial screen of such an experiment would most likely result in a designation of not highly relevant to assess the hormesis hypothesis. However, the study would be retained for further evaluation within a weight-of-evidence context, based on the observation of the low-dose stimulation. At present this experiment would be most consistent with either a low or not relevant evidence designation of hormesis. Neither categorical placement is convincing.

Figure 2B likewise depicts a study with a limited dose range (10-fold) with a limited number of doses. However in contrast to Figure 2A, a more striking stimulatory response is seen at the lowest dose, which is highly statistically significant. However, this study is limited by having only one dose showing a stimulatory response even though the response was impressive. A case can be made for either a low or moderate evidence classification of hormesis.

Figure 2C depicts a study with a markedly larger dose range (500-fold) and number of doses (seven), with three doses in the hypothetical hormetic zone (i.e., doses less than the NOEL). However, the magnitude of stimulation is very limited and the observed increases are not statistically significant. This experiment would probably be considered as no or low evidence of hormesis. It would of course be a relevant study because of the wide dosage range, the substantial number of doses, the inclusion of doses below the LOEL, and the observation, although inconclusive, of stimulation at low dose.

Figure 2D depicts a study with a very broad dose range (> 1000-fold) and a large number of doses (11), with a low-dose stimulatory response observed in seven doses in the hypothetical hormetic zone. In addition the results display considerable statistical

power. This type of study would receive a high evidence ranking.

Figure 2E depicts a study with a wide range of doses (> 500) and a large number of concentrations with adequate statistical power. However the data do not show any evidence of a low-dose stimulation. This study would receive a not relevant designation because it does not establish a NOEL nor does it have any doses below the NOEL.
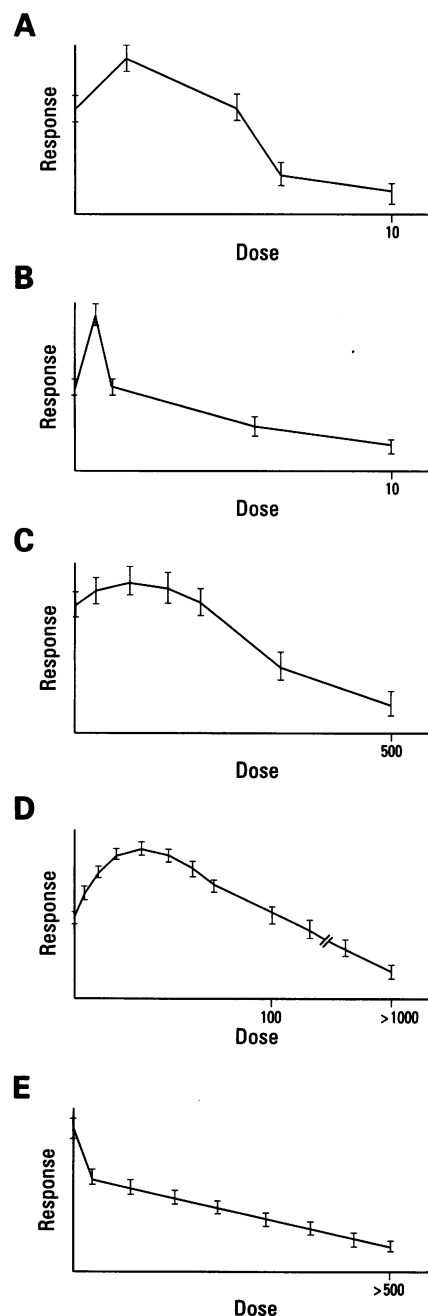
Figure 2. Dose–response curves illustrating various data sets evaluated for chemical hormesis.

Nature and Yield of Search Strategy

Table 1 summarizes the search strategy and yield. Computerized library searches were conducted on BIOSIS (Knight-Ridder Information, Mountain View, CA; 1969–1996), Chemical Abstracts (Knight-Ridder Information; 1967–1996), and Medline (Knight-Ridder Information; 1966–1996) using hormesis and the combination of U shaped plus dose response as key word descriptors. One hundred fifty-two publications were retrieved using hormesis as the key word descriptor; 165 publications were retrieved using the combination of U shaped plus dose response. Radiation hormesis was the subject of 104 of the 317 publications.

Based on information obtained from the initial searches described above, additional search strategies were employed using the same three databases and the following key word descriptors: low dose plus stimulation, beta curve plus dose response, adaptation plus pollution, and homeopathy. A total of 4058 articles was identified then reduced to 3272 following elimination of database replication of articles. Manual review of the 3272 abstracts revealed approximately 172 potentially relevant publications, the

majority of which were chemically oriented. Radiation studies comprised approximately 25% of the 172 articles.

A computerized library search conducted on the database Agricola (Knight-Ridder Information; 1970–September 1995) using the key word descriptors hormesis, U shaped plus dose response, and low dose plus stimulation revealed very few articles not already identified in the previous searches.

To include the most recent articles, computerized searches of the Current Contents Life Sciences and Agricultural, Biological, and Environmental Sciences databases (Institute for Scientific Information, Philadelphia, PA) for the time period 15 May 1995 through 5 June 1996 were conducted using the key word descriptors hormesis, U shaped plus dose response, low dose plus stimulation, adaptation plus pollution, and beta curve. Only a small number of new articles not included in the prior searches was identified.

Potentially relevant articles not included in the computerized library searches were obtained from extensive cross-referencing of primary sources.

Most recently additional search strategies were employed using BIOSIS,

Medline, and Chemical Abstracts and the following key word descriptors: doses plus sublethal, doses plus subtoxic, doses plus subthreshold, responses plus sublethal, responses plus subtoxic, and responses plus subthreshold. A total of 5569 articles was identified then reduced to 3776 following elimination of database replication of articles. Manual review of the 3776 abstracts revealed approximately 67 potentially relevant publications.

A computerized library search using the same key word descriptors listed above and the database Agricola (1970–September 1996) identified 230 articles. When reviewed approximately 25 were considered potentially relevant. The same key word descriptors were also used in computerized searches of the Current Contents Life Sciences and Agricultural, Biological, and Environmental Sciences databases for the time period 16 October 1995 through 7 October 1996 to include the most recent articles. Of the 214 abstracts identified, 27 new articles were considered potentially relevant.

Finally, computer searches of Science Citations (Institute for Scientific Information; 1990–1996) were conducted using authors' names Stebbing ARD and Luckey TD. Approximately 400 articles were identified, of which 149 were considered potentially relevant.

Results of Article Evaluation

Those studies placed within a high evidence category of chemical hormesis had the greatest number of total study doses (i.e., 6.3 on average) and doses in the so-called hormetic zone (i.e., 3.4 on average), followed by studies demonstrating moderate evidence and more distantly by studies demonstrating low evidence (Table 2).

The types of chemicals that induce hormetic effects represent a broad range of chemical classes (Table 3). The most studied

Table 1. Summary of computerized search strategy.

Key words	Databases	Abstracts retrieved, no	Potentially relevant, no
Hormesis	BIOSIS, Medline, Chemical Abstracts[a]	150	90
U shaped + dose response	BIOSIS, Medline, Chemical Abstracts	165	31
Low dose + stimulation Beta curve + dose response Adaptation + pollution Homeopathy	BIOSIS, Medline, Chemical Abstracts	3272	172
Hormesis U shaped + dose-response Low dose + stimulation	Agricola (1970–Sept 1995) Current Contents (15/5/95–6/5/96)	>200	24
Adaptation + pollution Beta curve	Current Contents (15/5/95–6/5/96)		
Dose response + sublethal Dose response + subthreshold	BIOSIS, Medline, Chemical Abstracts	3776	67
Dose response + subtoxic	Agricola (1970–Sept 1996) Current Contents (16/10/95–7/10/96)	230 214	25 27
Stebbing ARD	Science Citations (1990–Mar 1996)	207	84
Luckey TD	Science Citations (1990–Sept 1996)	200	65

[a]BIOSIS (1969–1996), Medline (1966–1996), Chemical Abstracts (1967–1996).

Table 2. Characteristics defining studies demonstrating high, moderate, low, and no evidence of hormesis.

Evidence of hormesis	Mean doses, no	Mean doses, no ≤ NOAEL	Inadequate doses, no	Inadequate dose range	Inadequate end point	Lack of statistical power
High	6.3	3.4	–	–	–	–
Moderate	5.5	2.8	–	–	–	–
Low	4.7	1.8	X	X	–	X
No	4.7	<1.8	X	X	X	X

Abbreviations: –, characteristic was generally not evident; X, characteristic was generally evident.

Table 3. Results of initial screening organized by agent.[a]

Agent	Percent
Alcohol and metabolites	6.2
Antibiotics	7.9
Auxin related	4.6
Hydrocarbons	3.4
Metals	29.6
Herbicides	7.2
Insecticides	6.1
Fungicides	1.5
Pesticides	2.9
Miscellaneous	30.6
Total	100.0

[a]High, moderate, and low data are combined.

Table 4. Results of initial screen organized by end point.

	High	Moderate	Low	Number	Percent
Growth	161	147	61	369	62.2
Metabolic effects	38	27	25	90	15.2
Longevity	21	5	5	31	5.2
Survival	13	18	3	34	5.7
Reproduction	7	18	9	34	5.7
Miscellaneous	8	22	5	35	5.8
Total	248	237	108	593	99.8

agents were metals, followed by alcohols, antibiotics, auxin-related compounds, and numerous biocidal agents. The range of hormetic responses is listed in Table 4 and indicates that the principal end point is growth, followed by metabolic changes (e.g., enzyme activity), longevity, and various reproductive indices.

Characteristics of the Chemical Hormetic Zone

To assess the characteristics of the chemical hormetic dose–response zone, experimental data were evaluated with respect to a) the dosage range of the hormetic zone (i.e., from the estimated dosage where the response starts to deviate from the control to the estimated dosage where the response begins to dip below the controls); b) the maximum stimulatory response (as a percentage greater than the control response); and c) the magnitude of dosage difference from the maximum stimulatory response and the estimated NOEL (Figure 3).

In general the hormetic dose–response range is usually within a 10-fold range. Stimulatory effects, however, have been reported over dosage ranges of two or more orders of magnitude as well as over a more narrow range of dosages depending on the agent, end point, and model assessed. The magnitude of stimulatory responses has been observed as high as several-fold but the majority of low-dose stimulations are

Figure 3. Dose–response curve depicting characteristics of the chemical hormetic zone. ZEP, zero equivalent point.

30 to 60% greater than the controls. The distance from the maximum stimulatory response to the NOEL is difficult to discern as it is a function of the number of doses employed, their variability in response, and the estimated value of the NOEL. Nonetheless, the distance between the maximum stimulatory response and the estimated NOEL is typically observed in the 3- to 6-fold range (i.e., the NOEL is about 3- to 6-fold greater than the maximum stimulatory response).

Hormesis as a General Biological Phenomenon

Hormetic responses are observed in numerous species from a broad range of taxonomic groups including microbes, plants, and animals (Table 5). These responses occur with a large number of chemicals representing a broad range of chemical classes (Table 3). Although Stebbing (2) focused principally on growth hormesis, the present report indicates that hormetic effects are observed in a broad range of biological end points that involve not only growth but survival, longevity, reproduction, and numerous metabolic and physiological responses (e.g., metallothionein synthesis, DNA synthesis, RNA synthesis, mitosis, oxygen consumption, altered hepatic foci, photosynthesis rate, tissue regeneration, immune response, stress protein synthesis, germination of seeds, etc.). Thus hormesis appears relatively common with respect to species, chemical, and biological end point.

The ability to generalize hormetic responses also extends to the descriptive nature of the dose–response phenomenon

itself. As Stebbing (2) noted earlier, when the data are precise and comprehensive, the points appear to fit a β-curve and have remarkable similarity with respect to the range and amplitude of response. However it should be emphasized that the developmental dynamics of the hormetic dose response over time have not been widely or systematically studied. For example, while Stebbing (2) found that the form of the curve varied during the course of the experiment with hydra, Calabrese and Howe (9) observed a consistent shape of the β-curve over 4 to 6 weeks in plant growth experiments.

Why is Hormesis Infrequently Observed?

If hormesis is believed to be relatively common, questions arise as to why it is not reported more frequently and why the Arndt–Schulz law failed to become established. The infrequent reports of hormesis are most likely attributable to a combination of factors, predominantly the issue of appropriate study design, along with the influence on safety evaluation, which emphasizes the upper end of the dose–response continuum (i.e., where higher concentrations establish toxic responses that can be used in chemical evaluation and risk assessment). The present conclusions support this assessment; a direct relationship has been shown between the strength of the evidence supporting hormesis and the number of doses, including both overall experimental number of doses and the number of doses in the hormetic zone. Furthermore, because the average range of the hormetic zone is about one order of magnitude this phenomenon is difficult to discern when wide dose intervals (e.g., > 10-fold) are used.

Predictive insight into the number of published articles potentially displaying hormesis may be derived as follows. Assuming 500,000 toxicology studies have been published this century (based on searches of Chemical Abstracts, Index Medicus, and BIOSIS), it is estimated that approximately 350,000 toxicology articles
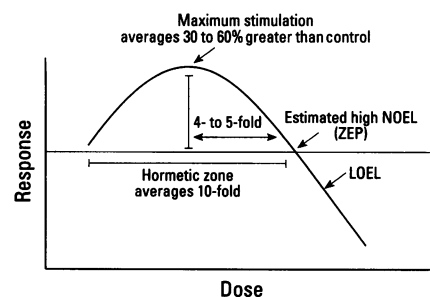
Table 5. Results of initial screen organized by test model.

	High	Moderate	Low	Number	Percent
Bacteria	17	27	11	55	9.3
Protozoa	7	9	2	18	3.0
Fungi	24	8	6	38	6.4
Plants	112	63	32	207	34.9
Animals	88	130	57	275	46.3
Total	248	237	108	593	99.9

have been published since 1966. Thus we assume for the sake of argument that 500,000 toxicology papers comprise the available pool for evaluation. If we also assume that 2% of these studies include six or more doses (10) then 10,000 studies may contain dose ranges adequate for hormesis evaluation. Of these 10,000 studies, based on the characteristics defining hormetic studies, approximately 10% (i.e., 1000) have three or more doses below the estimated NOEL. Further refinement of this estimation can be made by assuming that 90% of these 1000 studies have doses in the low-dose range within one to two orders of magnitude and close to the estimated NOEL (10).

These figures suggest that mammalian toxicologists may have had only limited direct interaction with the concept of hormesis, as only an estimated 900 potentially relevant studies exist. Therefore it is not surprising that toxicologists may view hormesis more as a belief than a phenomenon and that the Arndt–Schulz law (i.e., hormesis) fell into general disuse.

In addition to the low number of hormetic observations reported, Stebbing (2) suggested that the Arndt–Schulz Law fell into disuse because it lacked an explicit mechanism component. However, the concept of adaptation, a potentially important explanatory component for hormesis, has evolved for the most part independent of hormesis. Although numerous studies of adaptation exist, only a limited number address specific mechanisms applicable to chemically induced hormetic dose–response relationships. Nonetheless there are studies that have sought to mechanistically explain specific hormetic dose–response relationships.

Perhaps the most systematically assessed mechanism-based research has been in the area of herbicide-induced stimulatory effects. Hormetic responses have long been recognized by herbicide researchers who have conducted studies assessing not only the molecular basis for the response but also the effect of the plant species and age on the response.

A growing number of mammalian examples also exists where plausible explanatory mechanisms have been put forth to account for specific hormetic dose–response relationships (11–15).

The wide range of hormetic effects (e.g., increased growth, fecundity, longevity, and decreased disease incidence) suggests that these changes are fundamental and affect thousands of genes. This implies that hormetic mechanisms are likely to be operational in a very upstream location. Nevertheless investigators often focus on mechanisms more closely related to biological protection. For example, substantial evidence exists in numerous species that specific alterations in patterns of gene expression occur in response to toxicant exposure. Such responses can be sorted into two classes: those resulting in an enhanced metabolic capacity for detoxi-

fication (e.g., the cytochrome P450 gene family) and those that offer a more general protection against cellular damage caused by a wide variety of agents (e.g., heat shock or stress proteins).

Proposed Quantitative Evaluation Scheme

A quantitative scheme has been developed to provide a more objective and reproducible methodology for ranking studies with respect to hormetic potential. Criteria have been established and assigned point values based on: the number of experimental doses below the NOEL, experimental determination or estimation of the high NOEL, the statistical significance of the stimulatory response, the magnitude (percentage of control value) of the stimulatory response, and the reproducibility of data by other studies (Tables 6 and 7). Evidence of hormesis will be assessed by comparing the summation of point values to point ranges established for six evidence categories: high, moderate–high, moderate, low–moderate, low, and no–low (Table 8). Results of the application of this methodology and comparison with the current qualitative findings will be published elsewhere (16).

Summary

A goal of the present research is to create a database of studies demonstrating objective evidence of hormesis. It is hoped that this database, when complete, will enable the scientific community to evaluate more rigorously and efficiently the concept of hormesis with respect to its status as a biological hypothesis, its potential to be generalized, and its impact on environmental and human health.

The findings to date indicate that examples of low-dose stimulation consistent with β-curve characteristics are copious, diverse, independently derived, and reproducible. Yet despite the large number of such observations no long-term systematic effort has been made to uncover explanatory mechanisms, except in limited cases (e.g., herbicidal agents).

Table 6. Summary of study design criteria with assigned point values used in the quantitative evaluation of articles for evidence of chemical hormesis.

Number of doses below NOEL	Point value	NOEL determined	Point value
1	1	Yes	1
2	2	No	0
3	3		
4	4		
≥5	5		

Table 7. Summary of response criteria with assigned point values used in the quantitative evaluation of articles for evidence of chemical hormesis.

Number of doses statistically significant	Point value	Magnitude of response, % of control	Point value[a]
1	2	>110≤125%	0.5
2	4	>125≤150%	1
3	8	>150≤200%	2
>4	16	>200≤400%	3
		>400%	4

[a]The point value is multiplied by the number of experimental doses falling within the corresponding percentage range. For example, if an experiment has three doses exhibiting stimulatory responses within the 125 to 150% range, the total number of points will be $3 \times 1.0 = 3$.

Table 8. Summary of total point ranges for hormesis evidence categories used in the quantitative evaluation of articles for evidence of chemical hormesis.

Total point range	Hormesis evidence category
1–2	No to low
>2–8	Low
>8–12	Low to moderate
>12–16	Moderate
>16–20	Moderate to high
>20	High

A more objective and reproducible evaluation methodology for ranking studies with respect to hormetic potential is needed. The development of quantitative criteria based on study design, response, and reproducibility of findings is proposed and will be applied to the current database.

Furthermore, statistical simulations of dose–response relationships given various types of variability in control groups can provide important insight into the establishment of more quantifiable criteria in the evaluation of possible hormetic findings. The area of hormesis and its evaluation as a biological hypothesis has striking similarities to the evolving mathematical area of meta-analysis in epidemiology. In fact the application of meta-analysis techniques to the evaluation of hormetic response data is likely to yield significant advances.

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